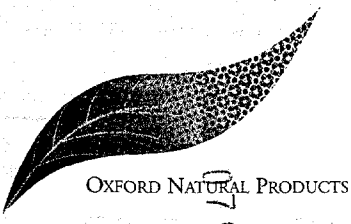

OXFORD NATURAL PRODUCTS

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville
MD 20852
USA

6th October 2000

Dear Sir

Guidance for Industry – Botanical Drug Products
Docket Number: OOD-1392

The FDA has kindly invited comments and suggestions on the above guidelines and I write to present an innnovative approach developed by Oxford Natural Products plc.

Oxford Natural Products plc is a technology and development company with specialist expertise in the field of natural products and particularly the development of botanical drugs. We welcome the publication of your draft guidelines, particularly the fact that FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic or highly purified drugs. We would like to take this opportunity to comment upon the draft regulations, specifically regarding the approach to the characterisation of botanical drug products, substances and raw materials, and the technology used in the chemistry, manufacturing and control of these materials.

As stated in your draft guidelines, "botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures". In many cases these complex mixtures have been shown to exhibit synergism. That is to say, the clinical effect of the complex mixture is greater than, or at least different from, the combined effect of the individual entities. This suggests multi-path activity both between chemical entities, and between those chemical entities and their biological targets (where they exist), which may, in fact, never be fully elucidated using reductionist analytical procedures. Crucially, the observed clinical outcome can be effectively linked to a "characterisation" of the whole extract.

If synergism exists, as seems to be the case in many botanical drug products, then attempting to identify active components is of little or no value. Indeed the very notion of an "active constituent" is likely to be misleading and unhelpful. It also seems clear that striving to identify a marker compound will never solve this problem either. Even if the marker can be shown to be reproducible, this does not indicate that the botanical drug product is consistent.

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OOD-1392

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Nevertheless, the ability to characterise or "fingerprint" the whole extract is vitally important. It allows the specific correlation of an observed clinical effect with a known material.

Oxford Natural Products plc is addressing the issue of characterisation by means which do not rely on orthodox "reductionist" approaches. The method and philosophy is outlined in the following paragraphs.

Recent advances in instrumental methods make it possible to generate meaningful fingerprints of the **whole** extract, without any intermediate steps that could unknowingly remove or alter some components of the extract. (For example, some components may irreversibly bind to a chromatographic stationary phase and never be detected.) Although there are a number of possible approaches, including mass spectrometry and near infrared spectroscopy, only high field hydrogen-1 NMR spectroscopy provides the right combination of sensitivity, robustness and (lack of) selectivity. Spectra obtained at high operating frequencies show increased sensitivity and signal dispersion such that very precise fingerprints may be generated. The technique generates large quantities of raw primary data that can be reduced to convenient levels and analysed using advanced statistical procedures such as principal component analysis (PCA). Appropriate computer software can in turn present powerful visual representations of real differences between samples.

Characterisation of the botanical drug materials by the use of hydrogen-1 NMR spectroscopy may not be sufficient in itself. Although this provides a detailed insight into the chemical composition of the material, it does not provide any information on its biological activity. The use of proteomics, to study the modification of protein expression in appropriate target cells, demonstrates the biological activity of the botanical drug material, without the need for any separation or understanding of the mechanism(s) of action. This information is complementary to the hydrogen-1 NMR spectroscopy data.

Thus, a biological effect initiated, for example, by an enzyme inhibitor will ultimately cause a change in protein expression. An analogous change will also be induced by an agent acting by any biological mechanism. Importantly, an extract containing more than one active molecule will show a constant and dose-dependent pattern of change of protein expression that is the overall effect of these several (and perhaps separate) mechanisms. This change is characteristic of the effect of a particular plant extract on a defined target cell and, as such, can be used as a biological fingerprint representing a total pharmacological effect, without knowledge of the individual effects contributing to the final total pattern.

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6th October 2000

Dockets Management Branch (HFA-305)

The high resolving power and sensitivity of high field hydrogen-1 NMR spectroscopy make it a powerful tool in dealing with botanical drug materials. However, even slight changes in the botanical drug raw material, substance or product will be identified by the technique and will change the corresponding "fingerprint". Clearly all natural products show variability in their precise chemical composition, but this does not necessarily render them unsafe or ineffective. Factors with the potential to induce such "fingerprint" modifications include changes in the climatic conditions during growth of the raw material, or storage temperature, or processing methodology, so that the "fingerprint" is frequently unique to a given batch of product. Understanding the cause of this variability is a fundamental requirement if high resolution fingerprints are to be an effective tool in a regulatory and commercial setting.

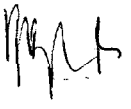
It is necessary thus to define acceptable limits of variation for the whole extract or a specification within which the material must fall. The combination of hydrogen-1 NMR spectroscopy, proteomics and a detailed understanding of the actual production processes and conditions at all points in the supply chain is capable of defining such a specification. By capturing detailed, process level information throughout the supply chain it is possible to determine cause and effect relationships between material fingerprints and production events. With this information critical control points can be defined and appropriate monitoring regimes implemented. The company has developed a proprietary data management system known as PhytoTrack to carry out this comprehensive traceability function.

In summary, Oxford Natural Products plc has assembled a team of scientists and technologists with relevant skills and expertise to address this complex but vital issue. Enclosed with this letter is an information pack describing the activities of Oxford Natural Products plc in more detail.

I would welcome the opportunity of an early meeting with relevant FDA staff in order to discuss the suitability and applicability of our approach with respect to the development of botanicals and its role in future guidelines and even registration procedures.

I look forward to hearing from you.

Yours sincerely



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IBC

DATE	CONSIGNMENT NUMBER
6/10/00	60235

FROM:

COMPANY

STREET — **Oxford Natural Products Plc**
No 1, St Giles

CITY — **Oxford**

COUNTRY — **OX1 3JS**

TO: Dockets Management Branch (HFA-305)

COMPANY Food & Drug Administration

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